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- Annual Report
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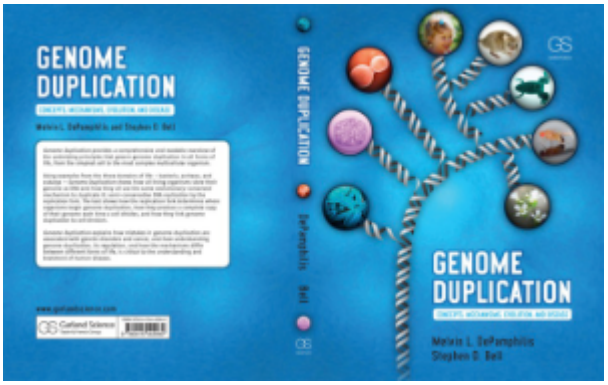

Figure 1: Genome Duplication (Concepts, Mechanisms, Evolution and Disease)

Figure 2: Ultra High Throughput Robotic Screening System at the NIH Chemical Genomics Center

The Section on Eukaryotic DNA Replication focuses on how genome duplication is regulated during early embryogenesis in mammals, particularly during the formation and differentiation of trophoblast and embryonic stem cells. Previous work focused on characterization of DNA replication origins and the proteins that select which origins become active and when they become during cell proliferation. These studies led to the discovery that initiation of DNA replication occurs at specific sites in mammalian chromosomes, and that the 'origin recognition complex' cycles on and off chromatin during cell division, thereby providing a mechanistic foundation for the 'Jesuit Model' of origin specification during animal development. More recently, turned our attention to the mechanism by which trophoblast stem (TS) cells exit their mitotic cell cycle in order to differentiate into the polyploid trophoblast giant (TG) cells essential for embryo implantation and placentation. This work revealed that the Tead4 transcription factor specifies the trophectoderm linage, and the DNA damage response protein kinase Chk1 prevents premature expression of p57/Kip2 in TS cells. P57 is cyclin-dependent protein kinase-specific inhibitor that is unique to mammals and that triggers differentiation of TS cells into TG cells by selectively inhibiting Cdk1, the enzyme responsible for driving cells into mitosis. This mechanism operates like a G2 phase restriction point in that it responds to changes in mitogenic factors. Finally, we are developing a novel strategy for selectively killing cancer cells through the induction of unscheduled DNA replication by inhibiting the activity of Geminin, a small protein unique to the metazoa that helps to restrict genome duplication to once per cell division. We then developed high throughput screens to identify a number of small molecules and siRNAs that selectively induced DNA re-replication in cancer cells in vitro. Their targets and mechanisms of action will be determined, as well as their ability to function in mice as chemotherapeutic agents against cancer.

Selected Publications

- Ullah Z, de Renty C, DePamphilis ML. Checkpoint kinase 1 prevents cell cycle exit linked to terminal cell differentiation. (2011) Mol Cell

Biol. 31: 4129-43.
- DePamphilis ML, Bell SD. Genome Duplication (concepts, mechanisms, evolution and disease). (2010) Garland Science, London and New York.
- Bhattaram P, Penzo-Mendez A, Sock E, Colmenares C, Kaneko KJ, Vassilev A, Depamphilis ML, Wegner M, Lefebvre V. Organogenesis relies on SoxC transcription factors for the survival of neural and mesenchymal progenitors. (2010) Nat Commun 1: 9.
- Zhu W, Depamphilis ML. Selective killing of cancer cells by suppression of geminin activity. (2009) Cancer Res 69: 4870-4877.
- Ullah Z, Kohn MJ, Yagi R, Vassilev LT, DePamphilis ML. Differentiation of trophoblast stem cells into giant cells is triggered by p57/Kip2 inhibition of CDK1 activity. (2008) Genes Dev 22: 3024-3036.